



STIC Search Report

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STIC Database Tracking Number: 125533

TO: Kevin Weddington
Location: rem/4b87/4c70
Art Unit: 1614
Tuesday, June 29, 2004

Case Serial Number: 10/717738

From: Mary Hale
Location: Biotech/Chem Library
Rem 1D86
Phone: 2-2507

Mary.Hale@uspto.gov

Search Notes

Acidosis or acid base imbalance or acidity of bodily fluid

And

Insulin sensitizer

6 399658
metformin
insulin sensitizer
does not work.
WD 98 27982
SA 6/5/04

REM-4B87

Access DB#

125533

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: K. Weddington Examiner #: 68082 Date: 6-22-04

Art Unit: 1614 Phone Number 301 272-0587 Serial Number: 101717, 738

Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

MEY

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

Earliest Priority Filing Date: _____

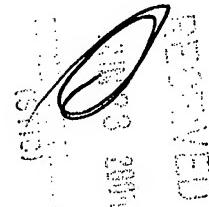
For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

A method for treating acidosis with an acid-base imbalance

~~metformin~~ insulin sensitizer.

metformin
thiazolidinedione
TZDs

acidity of bodily fluids



medicament
illness
drug
general

16:19
16:05-15

3-36
91-79
13-68
144-47

STAFF USE ONLY

Searcher: Chaley

Type of Search

NA Sequence (#)

Vendors and cost where applicable

STN

144.47

Weddington
10/29/77 38

=> fil medl,hcapl,biosis,embase,jicst,wplids;s (acidosis or acid base imbalance) and insulin sensit?

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	3.36	147.32
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L1	28 FILE MEDLINE
L2	26 FILE HCAPLUS
L3	22 FILE BIOSIS
L4	88 FILE EMBASE
L5	6 FILE JICST-EPLUS
L6	14 FILE WPIDS

TOTAL FOR ALL FILES

L7 184 (ACIDOSIS OR ACID BASE IMBALANCE) AND INSULIN SENSIT?

=> s l7(l)(treat? or therap? or medicament or drug)

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L1(L)(TREAT?)'

L8 21 FILE MEDLINE

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L2(L)(TREAT?)'

L9 8 FILE HCAPLUS

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L3(L)(TREAT?)'

L10 16 FILE BIOSIS

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L4(L)(TREAT?)'

L11 81 FILE EMBASE

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L5(L)(TREAT?)'

L12 6 FILE JICST-EPLUS

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L6(L)(TREAT?)'

L13 14 FILE WPIDS

TOTAL FOR ALL FILES

L14 146 L7(L)(TREAT? OR THERAP? OR MEDICAMENT OR DRUG)

=> s (acidosis or acid base imbalance) (l)insulin sensitiz?(l)(therap? or treat? or medicament or drug)

L15 2 FILE MEDLINE
L16 2 FILE HCAPLUS
L17 2 FILE BIOSIS
L18 4 FILE EMBASE
L19 0 FILE JICST-EPLUS
L20 1 FILE WPIDS

TOTAL FOR ALL FILES

L21 11 (ACIDOSIS OR ACID BASE IMBALANCE) (L) INSULIN SENSITIZ?(L) (THERAP
? OR TREAT? OR MEDICAMENT OR DRUG)

=> dup rem 121

PROCESSING COMPLETED FOR L21

L22 5 DUP REM L21 (6 DUPLICATES REMOVED)

=> d 1-5 cbib abs

L22 ANSWER 1 OF 5 MEDLINE on STN DUPLICATE 1
2001267939. PubMed ID: 11358680. Troglitazone, but not rosiglitazone, inhibits Na/H exchange activity and proliferation of macrovascular endothelial cells. de Dios S T; Hannan K M; Dilley R J; Hill M A; Little P J. (Cell Biology of Diabetes Laboratory, Baker Medical Research Institute, P.O. Box 6492, Victoria, Melbourne 8008, Australia.) Journal of diabetes and its complications, (2001 May-Jun) 15 (3) 120-7. Journal code: 9204583. ISSN: 1056-8727. Pub. country: United States. Language: English.

AB Diabetes is associated with a high level of mortality due to cardiovascular disease resulting from accelerated coronary artery atherosclerosis. A current focus for investigation of atherosclerotic mechanisms is the vascular endothelium since physical or functional injury may represent an initiating step for atherogenesis. Thiazolidinediones (TZDs) are the newest class of **drugs for the treatment** of insulin resistance and its metabolic consequences; they are peroxisome proliferator-activating receptor (PPAR)-gamma ligands that act as **insulin-sensitizing** agents. We are interested in the contribution of direct vascular actions to the clinical utility of these agents. We investigated the effect troglitazone and rosiglitazone on endothelial cell proliferation in low- and high-glucose media and further explored their action on the ubiquitous membrane transport system, the Na/H exchanger (NHE), which has been implicated in regulating the growth of vascular cells. Experiments were conducted in cultured bovine aortic endothelial cells (BAECs). Cell proliferation was assessed by cell counting, and NHE activity was determined in cells loaded with the pH-sensitive fluorescent dye, 2',7'-bis-(2-carboxyethyl)-5-(and-6)-carboxyfluorescein, acetoxyethyl ester (BCECF-AM). Troglitazone caused a dose-dependent inhibition of endothelial cell proliferation with approximately 50% inhibition at 10 microM. Troglitazone inhibited endothelial cell proliferation with similar potency under low- (5 mM) and high-glucose (25 mM) concentrations. Rosiglitazone had no significant effect on endothelial cell proliferation at concentrations of up to 100 microM under low- or high-glucose concentrations. The NHE inhibitor, 3-metyl sulfonyl-4-piperidinobenzoyl guanidine (HOE 694), caused dose dependent inhibition of BAEC proliferation, which was independent of the media glucose concentration. Acute exposure of cells to troglitazone (10 microM) and rosiglitazone (30 microM) during recovery from **acidosis** showed slight but significant ($P < .05$) inhibition of NHE activity by troglitazone, but no significant ($P > .05$) effect by rosiglitazone. Exposure of cells to either **drug** for 24 h revealed no chronic regulation of NHE activity. Our data demonstrate that troglitazone has similar actions in endothelial cells as in vascular

smooth muscle. The absence of rosiglitazone effects, a more potent PPAR-gamma activator, suggests that the observed actions of troglitazone may be at least partially independent of PPAR-gamma. The effects of troglitazone and rosiglitazone on endothelial cell proliferation and NHE activity, although contrasting, are consistent with a central signalling role of this transporter in cell proliferation.

- L22 ANSWER 2 OF 5 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
- 2002078670 EMBASE Efficacy of new drug therapies for diabetes in the elderly. Sinha B.; Nattrass M.. Dr. M. Nattrass, Diabetes Resource Center, Selly Oak Hospital, Raddlebarn Rd, Birmingham B27 6JD, United Kingdom. malcolm.nattrass@university-b.wmids.nhs.uk. Annals of Long-Term Care 9/6 (23-29) 2001.
Refs: 28.
ISSN: 1524-7929. CODEN: ALTCFF. Pub. Country: United States. Language: English. Summary Language: English.
- AB The treatment of diabetes in the elderly poses a challenge. If exercise and dietary measures fail, sulfonylureas may be considered as first-line therapy in the management of type 2 diabetes; however, they may be poorly tolerated in the elderly and carry a significant risk of severe hypoglycemia. Metformin (an insulin sensitizer) is quite useful in treating particularly overweight patients with type 2 diabetes, but in the elderly its use is limited by its potential to cause lactic acidosis in the presence of renal impairment. Newer drugs such as the insulin secretagogues, repaglinide and nateglinide, are as effective as sulfonylureas and have the advantage of causing less hypoglycemia. The thiazolidinediones, rosiglitazone and pioglitazone, are effective in improving glycemic control alone as well as in combination with metformin and sulfonylureas, but they may cause salt and water retention. Insulin treatment is often viewed as a last resort in the elderly, although whether this is fully justified may be debated as new approaches of combining insulin with oral agents raise hope.
- L22 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
2000:741906 Document No. 133:305606 Insulin sensitizers for improving ketosis, acidosis, and other conditions. Odaka, Hiroyuki; Suzuki, Masami (Takeda Chemical Industries, Ltd., Japan). PCT Int. Appl. WO 2000061127 A2 20001019, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-JP2413 20000413. PRIORITY: JP 1999-107119 19990414.
- AB The invention provides an agent for improving ketosis which comprises an insulin sensitizer, which has excellent action and low toxicity. The insulin sensitizers may also be used to improve acidosis and other conditions. The insulin sensitizers of the invention include e.g. pioglitazone hydrochloride.
- L22 ANSWER 4 OF 5 MEDLINE on STN DUPLICATE 3
95166749. PubMed ID: 7862618. Re-evaluation of a biguanide, metformin: mechanism of action and tolerability. Sirtori C R; Pasik C. (Centre E. Grossi Paoletti, University of Milano.) Pharmacological research : official journal of the Italian Pharmacological Society, (1994 Oct-Nov) 30 (3) 187-228. Ref: 139. Journal code: 8907422. ISSN: 1043-6618. Pub. country: ENGLAND: United Kingdom. Language: English.
- AB Metformin is a biguanide antidiabetic medication, that has been in use for over 30 years. Its mechanism of action, unknown until a few years ago, is

now linked to an improved peripheral sensitivity to insulin, through a stimulated tissue glucose uptake by a transporter linked system. Interest in metformin has been revived by the recent observation of a specific activity of this agent on some of the major traits of the so called 'polymetabolic syndrome' (or 'syndrome X'), characterized by: insulin resistance, hypertriglyceridemia, hypertension and reduced fibrinolytic activity. Metformin, in studies examining one or more of these, has been shown, possibly through its peripheral insulin sensitizing mechanism, to correct most of the major symptoms characterizing this insulin resistance syndrome. Metformin, similarly to the other biguanide phenformin, has been rated as potentially dangerous, because of the possible induction of lactic acidosis, in some cases with a fatal outcome. Metformin is, however, associated with a very low incidence of lactic acidosis because, differently from phenformin, it does not undergo liver metabolism and, as a consequence, there are no high-risk groups, displaying an impaired metabolic handling. In this review, in addition to an overall evaluation of the more recent data on the mechanism of action and clinical use of metformin, a detailed clinical analysis of all published cases of lactic acidosis is provided. These data indicate that the risk in metformin use is negligible, provided that care is taken when prescribing the drug to patients with suspected clinical risks of lactic acidosis.

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93352913 EMBASE Document No.: 1993352913. Using the oral hypoglycemic agents. Kinsley B.T.; Weir G.C.. Joslin Diabetes Center, 1 Joslin Place, Boston, MA 02215, United States. Endocrinologist 3/5 (321-329) 1993. ISSN: 1051-2144. CODEN: EDOCEB. Pub. Country: United States. Language: English. Summary Language: English.

AB The oral hypoglycemic agents are the main pharmacological treatment for noninsulin-dependent diabetes mellitus (NIDDM). At present, only the sulfonylureas are licensed for use in the United States. Metformin (a biguanide) is widely used overseas and is currently undergoing trials prior to possible release in this country. There is little difference in effectiveness between the various sulfonylureas when used in appropriate doses. On average, fasting blood glucose concentrations can be expected to fall by 50-70 mg/dL (3-4 mM/L). The maximum glucose-lowering effect is usually reached with a relatively low dose of the drug. Hypoglycemia is the main side effect of sulfonylurea therapy, especially in predisposed patients. Metformin may be useful in the treatment of obese NIDDM patients who have failed to achieve control with diet and exercise alone. It can also improve diabetic dyslipidemia by decreasing hypertriglyceridemia in subjects with NIDDM. Metformin does not cause hypoglycemia and, with careful patient selection, the risk of lactic acidosis with metformin therapy is low. Combination therapy with insulin and an oral hypoglycemic agent may offer some mild improvement in glycemic control. However, most studies suggest that optimal glycemic control is not achieved with combination therapy. Newer oral hypoglycemic agents, including the thiazolidinediones and the vanadium compounds, may act as 'insulin sensitizers' and are currently undergoing clinical testing.

=> => fil reg;e metformin/cn 5

COST IN U.S. DOLLARS

SINCE FILE ENTRY	TOTAL SESSION
27.54	174.86

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE ENTRY	TOTAL SESSION
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E1 1 METFOL-B/CN
E2 1 METFORAL/CN
E3 1 --> METFORMIN/CN
E4 1 METFORMIN CLOFIBRATE/CN
E5 1 METFORMIN HYDROCHLORIDE/CN

=> s e3;d ide can;e thiazolidinedione/cn 5
L23 1 METFORMIN/CN

L23 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 657-24-9 REGISTRY
CN Imidodicarbonimidic diamide, N,N-dimethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Biguanide, 1,1-dimethyl- (6CI, 8CI)
OTHER NAMES:
CN 1,1-Dimethylbiguanide
CN Dimethylbiguanide
CN DMGG
CN Fluamine
CN Flumamine
CN Gliguanid
CN Haurymelin
CN Melbin
CN Metformin
CN Metiguanide
CN N'-Dimethylguanylguanidine
CN N,N-Dimethylbiguanide
CN N,N-Dimethyldiguanide
CN N1,N1-Dimethylbiguanide
CN NNDG
CN Siofor
FS 3D CONCORD
MF C4 H11 N5
CI COM

Searched by: Mary Hale 571-272-2507 REM 1D86

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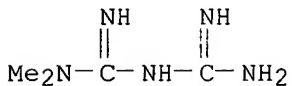
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Preprint

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

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RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); PROC (Process); PRP (Properties); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1426 REFERENCES IN FILE CA (1907 TO DATE)

23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

1429 REFERENCES IN FILE CAPLUS (1907 TO DATE)

19 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:12312

REFERENCE 2: 141:12310

REFERENCE 3: 141:7438

REFERENCE 4: 141:1598

REFERENCE 5: 141:262

REFERENCE 6: 140:418264

REFERENCE 7: 140:417962

REFERENCE 8: 140:412364

REFERENCE 9: 140:406798

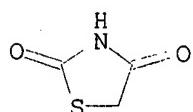
REFERENCE 10: 140:400444

E1 1 THIAZOLIDINEDICARBOXYLIC ACID, COMPD. WITH TRANS-4-((2-AMIN

E2 . O-3,5-DIBROMOPHENYL)METHYL)AMINO)CYCLOHEXANOL (1:1)/CN
 1 THIAZOLIDINEDICARBOXYLIC ACID, SALT WITH TRANS-4-(((2-AMINO-
 3,5-DIBROMOPHENYL)METHYL)AMINO)CYCLOHEXANOL (1:2)/CN
 E3 1 --> THIAZOLIDINEDIONE/CN
 E4 1 THIAZOLIDINEETHANIMINE, A-PHENYL-, HYDROBROMIDE/CN
 E5 1 THIAZOLIDINEOCTANOIC ACID, OCTYL-2-THIOXO-, METHYL ESTER/CN

=> s e3;d ide can
 L24 1 THIAZOLIDINEDIONE/CN

L24 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 2295-31-0 REGISTRY
 CN 2,4-Thiazolidinedione (8CI, 9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN 2-Thiazolin-4-one, 2-hydroxy- (7CI)
 CN Thiazolidinedione (6CI)
 OTHER NAMES:
 CN 2,4(3H,5H)-Thiazoledione
 CN 2,4-Dioxothiazolidine
 CN Glitazone
 CN NSC 6745
 CN U 25560
 FS 3D CONCORD
 MF C3 H3 N O2 S
 CI COM
 LC STN Files: ADISNEWS, AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS,
 BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS,
 CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, EMBASE, GMELIN*, HODOC*, IFICDB,
 IFIPAT, IFIUDB, MEDLINE, PROMT, PS, RTECS*, SPECINFO, SYNTHLINE,
 TOXCENTER, USPAT2, USPATFULL
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 Other Sources: EINECS**, NDSL**, TSCA**
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 DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent;
 Report
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 MSC (Miscellaneous); PREP (Preparation); PROC (Process); RACT (Reactant
 or reagent); USES (Uses); NORL (No role in record)
 RLD.P Roles for non-specific derivatives from patents: ANST (Analytical
 study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP
 (Properties); RACT (Reactant or reagent); USES (Uses)
 RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological
 study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP
 (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in
 record)
 RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological
 study); FORM (Formation, nonpreparative); PREP (Preparation); PROC
 (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



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1123 REFERENCES IN FILE CA (1907 TO DATE)

Searched by: Mary Hale 571-272-2507 REM 1D86

293 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1125 REFERENCES IN FILE CAPLUS (1907 TO DATE)
11 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:12312
REFERENCE 2: 141:12310
REFERENCE 3: 141:7118
REFERENCE 4: 141:923
REFERENCE 5: 140:429086
REFERENCE 6: 140:417934
REFERENCE 7: 140:416999
REFERENCE 8: 140:416998
REFERENCE 9: 140:416997
REFERENCE 10: 140:416996

=> fil medl,hcapl,biosis,embase,wplids,jicst;s (123 or 124 or metformin or thiazolidinedione or tzd!) and acidosis

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L25 297 FILE MEDLINE
L26 59 FILE HCAPLUS
L27 142 FILE BIOSIS
L28 684 FILE EMBASE
L29 17 FILE WPLIDS
L30 12 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L31 1211 (L23 OR L24 OR METFORMIN OR THIAZOLIDINEDIONE OR TZD!) AND ACIDO SIS

=> s 131 and (treat? or therap?)
L32 257 FILE MEDLINE
L33 49 FILE HCPLUS
L34 108 FILE BIOSIS
L35 638 FILE EMBASE
L36 17 FILE WPIDS
L37 10 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L38 1079 L31 AND (TREAT? OR THERAP?)

=> s 138 and (insulin or sensitiz?)
L39 82 FILE MEDLINE
L40 34 FILE HCPLUS
L41 52 FILE BIOSIS
L42 461 FILE EMBASE
L43 12 FILE WPIDS
L44 10 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L45 651 L38 AND (INSULIN OR SENSITIZ?)

=> s 138 and (insulin(2a)sensitiz?)
L46 3 FILE MEDLINE
L47 2 FILE HCPLUS
L48 1 FILE BIOSIS
L49 33 FILE EMBASE
L50 1 FILE WPIDS
L51 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L52 40 L38 AND (INSULIN(2A) SENSITIZ?)

=> s 152 not 122
L53 2 S L22
L54 1 FILE MEDLINE
L55 1 S L22
L56 1 FILE HCPLUS
L57 0 S L22
L58 1 FILE BIOSIS
L59 2 S L22
L60 31 FILE EMBASE
L61 0 S L22
L62 1 FILE WPIDS
L63 0 S L22
L64 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L65 35 L52 NOT L22

=> dup rem 165
PROCESSING COMPLETED FOR L65
L66 33 DUP REM L65 (2 DUPLICATES REMOVED)

=> d 1-33 cbib abs

L66 ANSWER 1 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
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2004165387 EMBASE Should insulin-sensitizing drugs be used in the treatment of polycystic ovary syndrome?. Cheang K.I.; Nestler J.E.. Dr. J.E. Nestler, Virginia Commonwealth University, Medical College of Virginia Campus, Richmond, VA 23298-0111, United States. nestler@hsc.vcu.edu. Reproductive BioMedicine Online 8/4 (440-447) 2004.

Refs: 58.

ISSN: 1472-6483. CODEN: RBOEA6. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Insulin resistance is a central feature of polycystic ovary syndrome (PCOS). Hyperinsulinaemia contributes to anovulation, hyperandrogenism, infertility and early pregnancy loss in women with PCOS. Chronic hyperinsulinaemia also predisposes women with PCOS to increased risks of diabetes and cardiovascular events. Current data indicate that metformin, either as monotherapy or in combination with clomiphene in clomiphene-resistant patients, is an effective treatment for anovulation in PCOS. Initial evidence also suggests that insulin sensitizers may have a role in preventing early pregnancy loss. Of the available insulin-sensitizing agents, metformin has been the agent most frequently studied in PCOS, and has the least undesirable pregnancy safety profile. Ameliorating the metabolic syndrome associated with insulin resistance in PCOS with metformin may also prevent long-term cardiovascular and diabetes complications, pending further evidence. Based on these data, metformin should be a first-line therapy for women with PCOS.

L66 ANSWER 2 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2004139959 EMBASE Intense Management of Diabetes Mellitus: Role of Glucose Control and Antiplatelet Agents. Mudaliar S.. Dr. S. Mudaliar, VA San Diego HealthCare System, Mail Code: V111G, 3350 La Jolla Village Drive, San Diego, CA 92161, United States. Journal of Clinical Pharmacology 44/4 (414-422) 2004.

Refs: 44.

ISSN: 0091-2700. CODEN: JCPCBR. Pub. Country: United States. Language: English. Summary Language: English.

AB Type 2 diabetes has now reached epidemic proportions across the world and is the cause of substantial morbidity and mortality. Patients with diabetes suffer from their microvascular complications of retinopathy (blindness), nephropathy (renal failure, dialysis), and neuropathy (neuropathic pain, trophic ulcers). However, ultimately, the majority of diabetics will die from macrovascular cardiovascular disease. Not only does cardiovascular disease develop earlier in the presence of diabetes, mortality from cardiovascular disease is increased by a factor of two to three in persons with diabetes as compared with the general population. To reduce this increased risk, a multifactorial approach to the management of type 2 diabetes has been advocated. The American Diabetes Association recommends not only good glycemic control but also identification and aggressive treatment of associated cardiovascular risk factors, with more stringent target levels for lipids and blood pressure than those recommended for the general population. Studies have shown that an intensified and goal-oriented approach to the treatment of type 2 diabetes addressing tight glucose control, optimal lipid and blood pressure management and the use of antiplatelet agents like aspirin reduces cardiovascular events, as well as nephropathy, retinopathy, and neuropathy.

L66 ANSWER 3 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2004116164 EMBASE HIV-associated lipodystrophy: Pathogenesis, prognosis, treatment, and controversies. Koutkia P.; Grinspoon S.. P.

Koutkia, Massachusetts General Hospital, Prog. Nutritional Metab. N., Harvard Medical School, 55 Fruit Street, Boston, MA 02114, United States. Annual Review of Medicine 55/- (303-317) 2004.

Refs: 76.

ISSN: 0066-4219. CODEN: ARMCAH. Pub. Country: United States. Language: English. Summary Language: English.

AB Potent antiretroviral agents markedly suppress HIV and have dramatically improved the clinical course, prognosis, and survival of HIV-infected patients. Unfortunately, highly active antiretroviral **therapy** is often compromised by metabolic complications, including insulin resistance, dyslipidemia, and fat redistribution. Together these changes have been termed the HIV-lipodystrophy syndrome, which is estimated to affect a majority of patients **treated** with potent combination antiretroviral **therapy**. Routine testing of fasting glucose is recommended for all HIV-infected patients, particularly those who are obese; have a family history of diabetes mellitus, or are receiving protease inhibitor **therapy**. Preliminary investigations have demonstrated the potential utility of insulin-sensitizing agents and lipid-lowering **therapies** to ameliorate these metabolic disturbances. Patients with HIV infection who demonstrate fat redistribution and develop hyperinsulinemia and dyslipidemia may be at increased risk of cardiovascular disease. However, the long-term effects on cardiovascular disease have not yet been determined.

L66 ANSWER 4 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2004149432 EMBASE [SFC/ALFEDIAM guidelines on the management of the diabetic patient seen by a cardiologist]. RECOMMANDATIONS SFC/ALFEDIAM SUR LA PRISE EN CHARGE DU PATIENT DIABETIQUE VU PAR LE CARDIOLOGUE. Charbonnel B.; Bouhanick B.; Le Feuvre C.; Charbonnel B.; Bouhanick B.; Le Feuvre C.; Bauduceau B.; Danchin N.; Gautier J.-F.; Grimaldi A.; Henry P.; Paillard F.; Pallo D.; Piot C.; Sabouret P.. Archives des Maladies du Coeur et des Vaisseaux 97/3 (229-249) 2004.

Refs: 77.

ISSN: 0003-9683. CODEN: AMCVAN. Pub. Country: France. Language: French.

L66 ANSWER 5 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2004081051 EMBASE Comparison of pioglitazone and **metformin** efficacy using homeostasis model assessment. Nagasaka S.; Aiso Y.; Yoshizawa K.; Ishibashi S.. Dr. S. Nagasaka, Div. of Endocrinology and Metabolism, Jichi Medical School, Yakushiji 3311-1, Minami-kawachi, Tochigi 329-0498, Japan. sngsk@jichi.ac.jp. Diabetic Medicine 21/2 (136-141) 2004.

Refs: 26.

ISSN: 0742-3071. CODEN: DIMEEV. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Aims: To compare clinical efficacy of two different insulin sensitizers, pioglitazone and **metformin**, and to reveal factors that influence the clinical efficacy. Methods: Seventy-eight Japanese subjects with Type 2 diabetes mellitus poorly controlled with sulphonylureas [38 men and 40 women, aged 57 ± 9 years, body mass index 25.2 ± 1.4 kg/m², and HbA(1c) $8.3 \pm 0.6\%$ (means \pm SD)] were randomly assigned to groups for the addition of either pioglitazone or **metformin** and followed up for 4 months. A decrease in HbA(1c) levels was compared with baseline factors including homeostasis model assessment of insulin sensitivity (HOMA-R) and β -cell function (HOMA- β) with 71 subjects who completed the study. Results: The overall decrease in HbA(1c) levels was similar for the pioglitazone ($-1.2 \pm 0.2\%$) and **metformin** ($-1.3 \pm 0.1\%$) groups. In the pioglitazone group, the decrease in HbA(1c) levels was negatively correlated with baseline HOMA-R ($r = -0.698$, $P < 0.0001$) and HOMA- β .

($r = -0.680$, $P < 0.0001$). In contrast, the decrease was positively correlated with baseline HOMA- β ($r = 0.556$, $P = 0.0004$) in the metformin group. Multivariate analysis revealed that either HOMA-R or HOMA- β was a main determinant of the decrease in HbA(1c) levels in the pioglitazone group. In the metformin group, baseline levels of fasting glucose were also included as an independent determinant in addition to HOMA- β . The subjects with greater HOMA-R (≥ 4.0) or HOMA- β ($\geq 40\%$) displayed better response to pioglitazone than to metformin, and vice versa. Conclusions: In Type 2 diabetic subjects poorly controlled with sulphonylureas, addition of pioglitazone or metformin resulted in a comparable reduction in HbA (1c) levels. Subjects with greater insulin resistance or preserved β -cell function displayed better response to pioglitazone, whereas subjects with reduced β -cell function displayed better response to metformin.

L66 ANSWER 6 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN

2004192102 EMBASE Metformin: Its botanical background. Bailey C.J.; Day C.. Dr. C.J. Bailey, Diabetes Group, Life and Health Sciences, Aston University, Birmingham B4 7ET, United Kingdom. c.j.bailey@aston.ac.uk. Practical Diabetes International 21/3 (115-117) 2004.

Refs: 33.

ISSN: 1357-8170. CODEN: PDINFY. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB This article traces the roots of the antihyperglycaemic biguanide metformin from the use of Galega officinalis (goat's rue or French lilac) as a herbal treatment for the symptoms of diabetes. G. officinalis was found to be rich in guanidine, as a substance with blood glucose-lowering activity that formed the chemical basis of metformin. This insulin sensitising drug was introduced in 1957. Copyright .COPYRGT. 2004 John Wiley & Sons, Ltd.

L66 ANSWER 7 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2004178767 EMBASE Assessment and therapy of selected endocrine disorders. Connery L.E.; Coursin D.B.. Dr. L.E. Connery, Depts. Surg., Int. Med., and Anesth., Long Island Jewish Medical Center, 270-05 76th Avenue, New Hyde Park, NY 11040, United States. lconnery@charter.net. Anesthesiology Clinics of North America 22/1 (93-123) 2004.

Refs: 48.

ISSN: 0889-8537. CODEN: ACNAEH.

Publisher Ident.: S 0889-8537(03)00111-1. Pub. Country: United States. Language: English. Summary Language: English.

AB Diabetes remains the most commonly encountered endocrinopathy with the incidence of type 2 doubling in the past decade. The prevalence of diabetes is projected to continue to increase dramatically over the next several decades unless major public health initiatives are successful in stemming this growth. Both type 1 and 2 diabetics more frequently require surgical and critical care than their non-diabetic counterparts. Type 1 and 2 diabetics also sustain greater perioperative morbidity and mortality. Careful preoperative assessment and appropriate perioperative intervention may limit this. There is increasing evidence that maintenance of normal blood glucose in the perioperative period and during critical illness is beneficial for diabetic and non-diabetic patients. More data will hopefully be forthcoming to substantiate recent reports and identify the mechanisms of improved outcome. Thyroid disease remains a commonly encountered pathology that is more readily identified and controlled in the modern era of radioimmune assays of thyroid hormone and successful medical and surgical therapies. Severe hypothyroidism and thyroid storm are associated with significant increases in perioperative morbidity and mortality. Recognition of these entities or those at risk

for developing them post operatively is crucial in initiating timely and effective **therapy**. Primary AI is uncommon, but results in glucocorticoid and mineralocorticoid deficiency. Tertiary AI is far more common, most often secondary to iatrogenic **therapy** with exogenous glucocorticoids for the management of chronic diseases such as connective tissue disorders, anti-rejection regimes, and severe asthma. Glucocorticoid replacement or supplementation is needed on a case-by-case basis and should be individualized based on chronic steroid dose, duration, and stress of the surgical procedure. Perioperative steroid dosing regimes now recommend lower doses for shorter periods than previously suggested. More recently AI has been recognized in two populations, elderly patients undergoing major surgery and a subgroup of patients with septic shock. Timely diagnosis using synthetic ACTH stimulation testing and stress glucocorticoid, and possibly mineralocorticoid **therapy**, seems to reverse these processes and improve recovery. Although uncommon, patients with pheochromocytoma who undergo open or laparoscopic resections remain diagnostic and **therapeutic** challenges. Perioperative outcome seems to have improved, in part, related to newer **therapies** and less invasive surgeries when indicated. The appropriate preoperative assessment and management of patients with various endocrinopathies is important to optimize outcome and limit avoidable complications. Hopefully additional evidence based guidelines will be forthcoming particularly in caring for the ever increasingly encountered perioperative diabetic.

L66 ANSWER 8 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2004207744 EMBASE Combination **treatment** with insulin and oral agents in type 2 diabetes mellitus. Burke J.. Dr. J. Burke, Barnet General Hospital, Thames House, Wellhouse Lane, Barnet, Hertfordshire EN5 3DJ, United Kingdom. john.burke@barnet-chase-tr.nhs.uk. British Journal of Diabetes and Vascular Disease 4/2 (71-76) 2004.
Refs: 35.
ISSN: 1474-6514. CODEN: BJDVAI. Pub. Country: United Kingdom. Language: English.

L66 ANSWER 9 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2004122178 EMBASE A Comparison of Agents Used to Manage Type 2 Diabetes Mellitus: Need for Reappraisal of Traditional Approaches. Bell D.S.H.. Dr. D.S.H. Bell, 1808 7th Avenue South, Birmingham, AL 35294, United States. dbell@endo.dom.uab.edu. Treatments in Endocrinology 3/2 (67-76) 2004.
Refs: 94.

ISSN: 1175-6349. CODEN: TERNAN. Pub. Country: New Zealand. Language: English. Summary Language: English.

AB In patients with type 2 diabetes mellitus, the traditional method of initiating **therapy** with a sulfonylurea and increasing the dosage until maximum levels are reached before adding an insulin-sensitizing agent has persisted and should be re-evaluated. Similarly, the current practice of starting **therapy** with one agent and increasing to maximum dosage before adding a second agent, rather than starting with combination **therapy**, also needs to be addressed. There is much evidence to suggest that initiating **therapy** with lower doses of two agents that have complementary effects can increase the overall efficacy and decrease the incidence of adverse effects. Clearly, there is a need for a paradigm shift away from the traditional approach of **therapy** using insulin secretagogues to a more pathophysiologic approach using an insulin-sensitizing agent, such as the thiazolidinediones. The thiazolidinediones have been shown to reduce insulin resistance, improve the ability of β -cells to produce insulin, and decrease cardiac risk factors. By reducing insulin resistance, improving glycemic

control, and preserving β -cell function with a **thiazolidinedione** early in the course of **therapy**, it is likely that durable glycemic control will be achieved and both microvascular and macrovascular complications may be reduced. Furthermore, early use of an **insulin-sensitizing agent** either alone or in combination is expected to improve both acute and long-term outcomes in patients with type 2 diabetes.

L66 ANSWER 10 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2004040013 EMBASE Oral Antidiabetic Agents: A Comparative Review. Koski R.R.. Dr. R.R. Koski, 1655 S. Westwood Circle, Ishpeming, MI 49849, United States. rkoski@mgh.org. Journal of Pharmacy Practice 17/1 (39-48) 2004. Refs: 33.

ISSN: 0897-1900. CODEN: JPPREU. Pub. Country: United States. Language: English. Summary Language: English.

AB Type 2 diabetes mellitus is a chronic disease characterized by insulin resistance, impaired insulin secretion, and/or increased hepatic glucose production. The mainstays of drug **treatment** are the oral antidiabetic agents. Insulin is usually reserved for patients who do not achieve fasting plasma glucose of A1C goals with or cannot tolerate the oral antidiabetic agents. There are 5 classes of oral antidiabetic agents available in the United States: sulfonylureas, biguanides, alpha-glucosidase inhibitors, **thiazolidinediones**, and non-sulfonylurea secretagogues. They have differences and similarities with respect to their pharmacology and role in diabetes. This article reviews the pharmacology, efficacy, safety, and selection of the oral agents used to **treat** type 2 diabetes mellitus.

L66 ANSWER 11 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2004121486 EMBASE Type 2 diabetes mellitus: What is the optimal **treatment** regimen?. Bell D.S.H.. D.S.H. Bell, Department of Medicine, University of Alabama at Birmingham, 1808 Seventh Avenue South, Birmingham, AL 35294, United States. American Journal of Medicine 116/5 SUPPL. 1 (23S-29S) 8 Mar 2004. Refs: 46.

ISSN: 0002-9343. CODEN: AJMEAZ.

Publisher Ident.: S 0002-9343(03)00673-9. Pub. Country: United States. Language: English. Summary Language: English.

AB **Treatment** options for type 2 diabetes mellitus currently consist of **insulin sensitizers**, α -glucosidase inhibitors, secretagogues, and insulin. However, the emphasis on initial **therapy** has been shifting from secretagogues and α -glucosidase inhibitors to **insulin sensitizers** such as metformin and the **thiazolidinediones** (TZDs). This article outlines the benefits of **treatment** with sensitizers vis a vis α -glucosidase inhibitors and secretagogues as part of a comprehensive **treatment** algorithm for type 2 diabetes. Secretagogues and α -glucosidase inhibitors effectively lower plasma glucose levels only, whereas **insulin sensitizers** reduce several important cardiac risk factors in addition to reducing plasma glucose levels. TZDs, in particular, are also beneficial for their ability to preserve or even rejuvenate pancreatic β -cell function. The **treatment** algorithm has a layered approach, beginning with a combination of **insulin-sensitizer therapy** and incrementally progressing to triple oral **therapy** with the addition of secretagogues and, if necessary, the addition of subcutaneous insulin to maintain glycemic control. .COPYRGT. 2004 by Excerpta Medica, Inc.

L66 ANSWER 12 OF 33 MEDLINE on STN

2003345779. PubMed ID: 12877089. **Insulin-sensitizing agents: metformin and thiazolidinedione derivatives.**
Satoh Jo. (Division of Molecular Metabolism and Diabetes, Tohoku University Graduate School of Medicine.) Nippon rinsho. Japanese journal of clinical medicine, (2003 Jul) 61 (7) 1224-9. Ref: 20. Journal code: 0420546. ISSN: 0047-1852. Pub. country: Japan. Language: Japanese.

AB Both **metformin** and **thiazolidinedione** derivatives (**TZDs**) improve insulin resistance, a major pathogenesis of type 2 diabetes, and decrease blood glucose levels without stimulating insulin secretion. **Metformin** inhibits glucose output from the liver, while **TZDs** increase glucose utilization in the peripheral tissues. In addition, there has been indicated that these agents ameliorate metabolic syndrome beyond glucose-level lowering. Molecular targets of these agents have recently been revealed; AMP-activated protein kinase (AMPK) for **metformin** and adiponectin, while PPAR gamma for **TZDs** which induce gene expression of adipocyte glycerol kinase and adiponectin. **Insulin-sensitizing** agents are clinically useful for obese diabetic patients with insulin resistance. However, periodical examinations are necessary to avoid serious adverse effects such as lactic acidosis, although rare, by **metformin** and liver injury by **TZDs**.

L66 ANSWER 13 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2003342770 EMBASE Current perspectives in polycystic ovary syndrome.
Richardson M.R.. Dr. M.R. Richardson, University of Kansas Medical Center, Department of Obstetrics, Div. Repro. Endocrinol./Infertility, 3901 Rainbow Blvd., Kansas City, KS 66160, United States. mrichardson@kumc.edu. American Family Physician 68/4 (697-704) 15 Aug 2003.

Refs: 35.

ISSN: 0002-838X. CODEN: AFPYAE. Pub. Country: United States. Language: English. Summary Language: English.

AB Polycystic ovary syndrome has been viewed primarily as a gynecologic disorder requiring medical intervention to control irregular bleeding, relieve chronic anovulation, and facilitate pregnancy. A large body of evidence has demonstrated an association between insulin resistance and polycystic ovary syndrome. The former condition has an established link with long-term macrovascular diseases such as type 2 diabetes mellitus, hypertension, and atherosclerotic heart disease, consequences that also are observed in women with polycystic ovary syndrome. In addition, chronic anovulation predisposes women to endometrial hyperplasia and carcinoma. The purpose of this review is to examine the clinical course of this syndrome, which spans adolescence through menopause, and suggest a simple and cost-effective diagnostic evaluation to screen the large numbers of women who may be affected. **Therapy**, which should be individualized, should incorporate steroid hormones, antiandrogens, and **insulin-sensitizing** agents. Weight loss by way of reduced carbohydrate intake and gentle exercise is the most important intervention; this step alone can restore menstrual cyclicity and fertility, and provide long-term prevention against diabetes and heart disease. **Treatment** alternatives should be directed initially toward the most compelling symptom. Longitudinal care is of paramount importance to provide protection from long-term sequelae.
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L66 ANSWER 14 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2003444940 EMBASE Polycystic ovary syndrome, hyperandrogenism, and insulin resistance. Zácur H.A.. Dr. H.A. Zácur, Department of Gynecology, Div. of Reproductive Endocrinology, Johns Hopkins Univ. Sch. of Medicine, 600 North Wolfe Street/Phipps 247, Baltimore, MD 21287, United States. hzacur@jhmi.edu. Infertility and Reproductive Medicine Clinics of North

America 14/4 (517-527) 2003.

Refs: 58.

ISSN: 1047-9422. CODEN: IRMCF8. Pub. Country: United States. Language: English. Summary Language: English.

AB Results from recent basic and clinical research investigations have greatly improved our understanding of insulin resistance in general and insulin resistance associated with PCOS in particular. With this understanding has come the possibility of using new methods to treat PCOS. This is particularly true when discussing the use of insulin-sensitizing drugs. Caution must be exercised in using these drugs because of unforeseen acute or remote adverse side effects. Postulated relationships among PCOS, hyperandrogenism, and insulin resistance do not completely solve the endocrinologic mystery of the patient with PCOS. For example, how does the partial destruction of the ovary (eg, wedge biopsy or ovary drilling by laser or cautery), which does not affect insulin resistance [58], result in ovulatory cycles? Why does the administration of excessive exogenous insulin in the case of the insulin-dependent diabetic fail to cause hyperandrogenism? Certainly, much remains to be learned about the reproductive endocrine disturbance we now call PCOS.

L66 ANSWER 15 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2003136394 EMBASE Insulin sensitizers. Zangeneh F.; Kudva Y.C.; Basu A.. Dr. A. Basu, Division of Endocrinology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States. basu.ananda@mayo.edu. Mayo Clinic Proceedings 78/4 (471-479) 1 Apr 2003.

Refs: 107.

ISSN: 0025-6196. CODEN: MACPAJ. Pub. Country: United States. Language: English. Summary Language: English.

AB Type 2 diabetes mellitus is an increasingly prevalent disorder associated with multiple metabolic derangements. Insulin resistance is the most prominent feature common in both type 2 diabetes and its associated metabolic abnormalities. Until 1995, the only therapeutic interventions available in the United States were the insulin secretagogues sulfonylureas and insulin. With the introduction of metformin in the United States in the mid-1990s and the subsequent advent of thiazolidinediones, an opportunity exists to address and directly reverse, at least in part, the defects in insulin action seen in individuals with type 2 diabetes. Evidence shows that insulin sensitizers not only have beneficial effects on glycemic control but also have multiple effects on lipid metabolism and atherosclerotic vascular processes that could prove to be beneficial. We discuss safety issues of these agents, their potential use in preventing onset and progression of diabetes, and their use in other related metabolic conditions such as polycystic ovary syndrome.

L66 ANSWER 16 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2003290295 EMBASE Insulin sensitizers for polycystic ovary syndrome. Baillargeon J.-P.; Iuorno M.J.; Nestler J.E.. Dr. J.E. Nestler, Medical College of Virginia, P.O.B. 980111, Richmond, VA 23298-0111, Canada. nestler@hsc.vcu.edu. Clinical Obstetrics and Gynecology 46/2 (325-340) 2003.

Refs: 56.

ISSN: 0009-9201. CODEN: COGYAK. Pub. Country: United States. Language: English. Summary Language: English.

AB PCOS has traditionally been regarded as an infertility disorder or cosmetic annoyance, but recent recognition of the prominent role of insulin resistance in the syndrome has revealed PCOS to be a metabolic disorder with systemic effects that is associated with a high risk for diabetes and cardiovascular disease. This dictates that treatment

modalities should focus not only on short-term amelioration of infertility or the syndrome's manifestations, but also on the diminution of its long-term adverse consequences on overall health. Evidence suggests that insulin-sensitizing drugs may accomplish these goals. This is in contrast to traditional therapy with OCPs, which may in fact increase the PCOS-associated risk for diabetes and heart disease.

L66 ANSWER 17 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2004171601 EMBASE Conservative management of gynecologic diseases:

Insulin sensitizing agents in polycystic ovary syndrome.

Diamanti-Kandarakis E.; Kandarakis H.A.. Prof. E. Diamanti-Kandarakis, Department of Medicine, University of Athens, Medical School, 1A-Zefyrou Ekali 145-78, Thens, Greece. akandara@otenet.gr. Annals of the New York Academy of Sciences 997/- (322-329) 2003.

Refs: 55.

ISSN: 0077-8923. CODEN: ANYAA. Pub. Country: United States. Language: English. Summary Language: English.

AB A contemporary "Pandora's box" could be the polycystic ovary syndrome (PCOS), containing several negative features for a woman: compromised looks, compromised fertility; increased metabolic risk factors; and compromised general health. During the past decade, the central importance of insulin resistance (IR) in the pathogenesis of this syndrome has been established. Several in vivo and in vitro studies have demonstrated this phenomenon, initially by the hyperinsulinemic response to oral glucose in obese and lean women with PCOS compared with weight-matched normal women, and subsequently with more sensitive techniques like euglycemic hyperinsulinemic clamp. In vitro studies have corroborated these findings, showing molecular defects at the postreceptor level of insulin action, such as increased serine phosphorylation and decreased phosphoinositol 3-kinase action. **Insulin sensitizers** are the group of therapeutic agents that hold some promise of helping women with polycystic ovary syndrome (PCOS), since the role of insulin resistance and hyperinsulinemia appear to be major contributors to the pathophysiology of the syndrome. The therapeutic approach with **insulin sensitizers** appears to have beneficial effects on the metabolic as well as on the reproductive abnormalities in women affected by PCOS. Finally, **insulin sensitizers** should be considered by all subspecialists who aim at a comprehensive management of patients with PCOS.

L66 ANSWER 18 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
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2004171600 EMBASE The management of polycystic ovary syndrome. Bruni V.; Dei M.; Pontello V.; Vangelisti P.. V. Bruni, Dept. Gynecol.-Perinatology Hum. R., University of Florence, Forence, Italy. vbruni@unifi.it. Annals of the New York Academy of Sciences 997/- (307-321) 2003.

Refs: 96.

ISSN: 0077-8923. CODEN: ANYAA. Pub. Country: United States. Language: English. Summary Language: English.

AB It is well known that subjects with polycystic ovary syndrome (PCOS) show very variable clinical and biochemical aspects. Considering long-term repercussions, two main disturbances, not always strictly related, need to be countered: hyperandrogenism and insulin resistance, with compensatory hyperinsulinemia. The aim of this review is to summarize therapeutic perspectives for PCOS, starting from basic approach, such as weight reduction and changes in lifestyle. The benefits of long-term use of oral contraceptives and the criteria of choice of the estrogen-progestin combinations are discussed. With severe hyperandrogenism, a pure antiandrogen should be added. The experiences with **insulin-sensitizing drugs**, especially metformin, are reviewed; while their beneficial role as an adjuvant to treatment of

ovulatory infertility has been well established, the effects of a long-term **treatment**, especially in very young patients, are still under debate. Current studies are testing the results of combinations of different **treatments** at low dosage; randomized comparative trials on the long-term efficacy of these approaches have yet to be scheduled.

L66 ANSWER 19 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2003371083 EMBASE Mechanisms and strategies for insulin resistance in acquired immune deficiency syndrome. Grinspoon S.. Dr. S. Grinspoon, Program in Nutritional Metabolism, LON 207, Massachusetts General Hospital, Boston, MA 02114, United States. Sgrinspoon@partners.org. Clinical Infectious Diseases 37/SUPPL. 2 (S85-S90) 1 Sep 2003.

Refs: 35.

- ISSN: 1058-4838. CODEN: CIDIEL. Pub. Country: United States. Language: English. Summary Language: English.

AB Abnormalities of glucose regulation, including impaired glucose tolerance and insulin resistance, are often seen among human immunodeficiency virus (HIV)-infected patients receiving highly active antiretroviral **therapy**. Insulin resistance in this population may result from antiviral medication directly impairing glucose uptake in the muscle, effects of HIV per se, or indirect effects, such as fat redistribution. Insulin resistance may increase the risk of coronary heart disease among this population of patients, in part by inhibiting normal thrombolysis. The optimal **treatment** for insulin resistance and impaired glucose intolerance in HIV-infected patients is not known, but preliminary studies have suggested that **metformin**, an **insulin sensitizing agent**, improves insulin sensitivity, blood pressure, and waist circumference. Initial studies of **thiazolidinediones** also suggest the potential utility of such agents to improve insulin sensitivity, decrease hepatic steatosis, and increase subcutaneous fat. Further studies are needed to determine the optimal **treatment strategy** for insulin resistance in this population.

L66 ANSWER 20 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
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2004165793 EMBASE Up-date Management of Non Responder to Clomiphene Citrate in Polycystic Ovary Syndrome. Amin M.; Abdel-Kareem O.; Takekida S.; Moriyama T.; El Aal G.A.; Maruo T.. Egypt. Kobe Journal of Medical Sciences 49/3-4 (59-73) 2003.

Refs: 100.

ISSN: 0023-2513. CODEN: KJMDA6. Pub. Country: Japan. Language: English. Summary Language: English.

AB Polycystic ovary syndrome (PCOS) is a heterogeneous disorder in which chronic anovulation is a common feature despite the presence of multiple micro-structures in the ovaries. A growing body of evidence has suggested that serum hyperinsulinemia contributes to the excess ovarian androgen secretion observed in women with PCOS. The standard **therapy** for anovulatory women with PCOS is oral administration of clomiphene citrate (CC). However, a significant proportion of women with PCOS fail to ovulate with the use of standard dosage of CC and are called CC-resistant PCOS. The recent introduction of the **insulin-sensitizing agents** as adjuvants to clomiphene citrate and gonadotropins has changed the **treatment strategy**. This is a comprehensive review of the literature, with an emphasis on the role of hyperinsulinemia in the pathogenesis of PCOS and on randomized controlled trials of the medical and surgical **treatment options** for women with CC-resistant PCOS. Although both standard and novel **treatments** were addressed in the present review, special attention was paid to the evidence in support of the recent introduction of **insulin-sensitizing**

agents in the management of anovulatory women with CC-resistant PCOS.

L66 ANSWER 21 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
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2003211769 EMBASE Prevention of type 2 diabetes: Are we ready?. Bouche C.; Goldfine A.B.. A.B. Goldfine, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215, United States. Allison.Goldfine@joslin.Harvard.Edu. Minerva Medica 94/1 (9-18) 2003.

Refs: 59.

ISSN: 0026-4806. CODEN: MIMEAO. Pub. Country: Italy. Language: English. Summary Language: English; Italian.

AB Type 2 diabetes is the most common metabolic disease. The cost of diabetes to the individual and to society, and the pandemic prevalence makes disease prevention of extreme importance. Persons with impaired glucose tolerance, modest elevations in blood glucose that remain below levels diagnostic for diabetes, are at increased risk of progression to overt diabetes. New studies evaluate the role of lifestyle interventions including diet and exercise, and the potential role of multiple classes of pharmaceutical agents including the **insulin sensitizers**, biguanides and thiazolidendiones, and carbohydrazine and lipase inhibitors in disease prevention of such high-risk individuals. Many of these strategies appear to be effective to delay, and perhaps prevent, the development of type 2 diabetes and thus should be considered for broader clinical application. Awareness of the extent of the problem and the potential benefits of prevention needs to be raised in both physicians and in the at high risk population.

L66 ANSWER 22 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
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2002457560 EMBASE Should patients with polycystic ovary syndrome be treated with metformin?: Benefits of insulin sensitizing drugs in polycystic ovary syndrome - Beyond ovulation induction. Stadtmauer L.A.; Wong B.C.; Oehninger S.. L.A. Stadtmauer, Howard/Georgeanna Jones Inst. Repro., 601 Colley Avenue, Norfolk, VA 23507, United States. stadtmla@evms.edu. Human Reproduction 17/12 (3016-3025) 1 Dec 2002.

Refs: 113.

ISSN: 0268-1161. CODEN: HUREEE. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The debate on metformin in polycystic ovary syndrome (PCOS) has mainly focused on its treatment for infertility in ovulation induction and menstrual cyclicity. Here we will summarize the data supporting the effect of metformin on improving hyperandrogenaemia and hyperinsulinaemia in PCOS patients. We propose that metformin benefits PCOS patients undergoing gonadotrophin therapy and IVF as well as ovulation induction. We also advocate the use of insulin sensitizing drugs to reduce miscarriage rates, and risks associated with coronary artery disease, gestational diabetes and obesity.

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2002329352 EMBASE Should patients with polycystic ovarian syndrome be treated with metformin? Proven and potential benefits. Seli E.; Duleba A.J.. A.J. Duleba, Dept. of Obstetrics and Gynecology, Yale University, School of Medicine, 333 Cedar Street, New Haven, CT 06520-8063, United States. antoni.duleba@yale.edu. Human Reproduction 17/9 (2230-2236) 2002.

Refs: 59.

ISSN: 0268-1161. CODEN: HUREEE. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The recognition of insulin resistance as a principal factor in the

pathogenesis of polycystic ovarian syndrome (PCOS) has led to the use of insulin-lowering agents, also called 'insulin-sensitizing drugs', for its treatment. The most extensively studied insulin-lowering agent in the treatment of PCOS is metformin: an oral antihyperglycaemic agent used initially in the treatment of type 2 diabetes mellitus. Metformin is effective in the treatment of PCOS-related anovulation and infertility. Moreover, preliminary evidence indicates that metformin may also be effective in decreasing the risk of early spontaneous miscarriage in women with PCOS. Metformin also appears to induce cardioprotective effects on serum lipids as well as plasminogen activator inhibitor (PAI)-1 and may decrease the risk of development of type 2 diabetes. The highly promising therapeutic profile of metformin is related to the role of this agent in controlling an important aetiological factor in the pathogenesis of PCOS: hyperinsulinaemia.

L66 ANSWER 24 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2002382064 EMBASE Troglitazone: The discovery and development of a novel therapy for the treatment of Type 2 diabetes mellitus.
Parker J.C.. J.C. Parker, Pfizer Global Research/Development, Groton Laboratories, 8220-0375, Eastern Point Road, Groton, CT 06340, United States. janice_c_parker@groton.pfizer.com. Advanced Drug Delivery Reviews 54/9 (1173-1197) 5 Nov 2002.

Refs: 181.

ISSN: 0169-409X. CODEN: ADDREP.

Publisher Ident.: S 0169-409X(02)00093-5. Pub. Country: Netherlands.

Language: English. Summary Language: English.

AB Prior to the introduction of troglitazone, it had been more than 30 years since the last significant improvement in antidiabetic therapy. In view of the pressing need for more effective oral agents for the treatment of Type 2 diabetes mellitus, troglitazone was granted priority review by the FDA and was launched in the USA in 1997. The first of the thiazolidinedione insulin sensitizing agents, troglitazone was quickly followed by rosiglitazone and pioglitazone. The glitazones proved to be effective not only in lowering blood glucose, but also to have beneficial effects on cardiovascular risk. Troglitazone was subsequently withdrawn because of concerns about hepatotoxicity, which appears to be less of a problem with rosiglitazone and pioglitazone. Recent insights into the molecular mechanism of action of the glitazones, which are ligands for the peroxisome proliferator-activated receptors, open the prospect of designing more effective, selective and safer antidiabetic agents. This document will review the history of troglitazone from discovery through clinical development. .COPYRGT. 2002 Elsevier Science B.V. All rights reserved.

L66 ANSWER 25 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2001242622 EMBASE Clinical importance of insulin secretion and its interaction with insulin resistance in the treatment of type 2 diabetes mellitus and its complications. Porte D. Jr.. D. Porte Jr., University of California, VA San Diego Healthcare System, Diabetes and Metabolism Division, 3350 La Jolla Village Drive, San Diego, CA 92161, United States. dporte@ucsd.edu. Diabetes/Metabolism Research and Reviews 17/3 (181-188) 2001.

Refs: 85.

ISSN: 1520-7552. CODEN: DMRRFM. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Type 2 diabetes primarily develops from pathogenic defects in the mechanisms of insulin secretion and hepatic and peripheral insulin action. The consequent disruption of normal glucose metabolism involves a number

of organ systems and is ultimately manifested in fasting and daytime hyperglycemia. Chronically elevated blood glucose concentrations determine the progression of the disease by further exacerbating insulin resistance and causing β -cell exhaustion in addition to decreasing their responsiveness to glucose. The β -cell secretory dysfunction is characterized by the lack of the early phase of glucose-induced insulin secretion and the insufficient and delayed late phase of secretion. Glycemic levels in patients with type 2 diabetes are directly related to the risk of developing microvascular and macrovascular complications, the main cause of the morbidity and mortality associated with this disease. The goal of treatment is to decrease the risk and delay the progression of these complications by improving glycemic control. Current oral antidiabetic agents, used as monotherapy or in combination, include traditional insulin secretagogues, insulin sensitizers and inhibitors of carbohydrate absorption. A greater understanding of the pathophysiology of type 2 diabetes and recent findings on the significance of meal-related glycemia to overall glycemic control are expanding the therapeutic options for treating this disease. Copyright .COPYRGT. 2001 John Wiley & Sons, Ltd.

L66 ANSWER 26 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 1

2001:330986 Document No.: PREV200100330986. Troglitazone, but not rosiglitazone, inhibits Na/H exchange activity and proliferation of macrovascular endothelial cells. de Dios, Stephanie T.; Hannan, Katherine M.; Dilley, Rodney J.; Hill, Michael A.; Little, Peter J. [Reprint author]. Cell Biology of Diabetes Laboratory, Baker Medical Research Institute, Melbourne, VIC, 8008, Australia. peter.little@baker.edu.au. Journal of Diabetes and its Complications, (May-June, 2001) Vol. 15, No. 3, pp. 120-127. print.

ISSN: 1056-8727. Language: English.

AB Diabetes is associated with a high level of mortality due to cardiovascular disease resulting from accelerated coronary artery atherosclerosis. A current focus for investigation of atherosclerotic mechanisms is the vascular endothelium since physical or functional injury may represent an initiating step for atherogenesis.

Thiazolidinediones (TZDs) are the newest class of drugs for the treatment of insulin resistance and its metabolic consequences; they are peroxisome proliferator-activating receptor (PPAR)-gamma ligands that act as insulin-sensitizing agents. We are interested in the contribution of direct vascular actions to the clinical utility of these agents. We investigated the effect troglitazone and rosiglitazone on endothelial cell proliferation in low- and high-glucose media and further explored their action on the ubiquitous membrane transport system, the Na/H exchanger (NHE), which has been implicated in regulating the growth of vascular cells. Experiments were conducted in cultured bovine aortic endothelial cells (BAECs). Cell proliferation was assessed by cell counting, and NHE activity was determined in cells loaded with the pH-sensitive fluorescent dye, 2',7'-bis-(2-carboxyethyl)-5-(and-6)-carboxyfluorescein, acetoxyethyl ester (BCECF-AM). Troglitazone caused a dose-dependent inhibition of endothelial cell proliferation with approximately 50% inhibition at 10 μ M. Troglitazone inhibited endothelial cell proliferation with similar potency under low- (5 mM) and high-glucose (25 mM) concentrations. Rosiglitazone had no significant effect on endothelial cell proliferation at concentrations of up to 100 μ M under low- or high-glucose concentrations. The NHE inhibitor, 3-metylsofonyl-4-piperidinobenzoyl guanidine (HOE 694), caused dose dependent inhibition of BAEC proliferation, which was independent of the media glucose concentration. Acute exposure of cells to troglitazone (10 μ M) and rosiglitazone (30 μ M) during recovery from acidosis showed slight but significant

(P<.05) inhibition of NHE activity by troglitazone, but no significant (P>.05) effect by rosiglitazone. Exposure of cells to either drug for 24 h revealed no chronic regulation of NHE activity. Our data demonstrate that troglitazone has similar actions in endothelial cells as in vascular smooth muscle. The absence of rosiglitazone effects, a more potent PPAR-gamma activator, suggests that the observed actions of troglitazone may be at least partially independent of PPAR-gamma. The effects of troglitazone and rosiglitazone on endothelial cell proliferation and NHE activity, although contrasting, are consistent with a central signalling role of this transporter in cell proliferation.

L66 ANSWER 27 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-679408 [66] WPIDS

AB WO 200061127 A UPAB: 20001219

NOVELTY - Agent comprises an **insulin sensitizer** optionally in combination with insulin.

ACTIVITY - Antibacterial; osteopathic; antianginal; cardiant; respiratory; antiemetic; gastrointestinal; anabolic; cerebroprotective.

MECHANISM OF ACTION - None given.

USE - For treating ketosis and acidosis, preferably diabetic ketosis or acidosis, or caused by a biguanide (claimed, hepatic glycogenesis, endocrine diseases, congenital metabolic disorders of carbohydrates or organic acids, acetonemia vomiting or gastrointestinal diseases, acidosis (claimed), disturbance of consciousness, coma or respiratory diseases, hyperosmolar nonketotic coma, infectious disease, diabetic osteoporosis, diabetic gangrene, xerostomia, lowered sense of hearing, angina pectoris, cerebrovascular disease or peripheral circulatory disturbance (all claimed).

The concentration of total ketone bodies in rats was 170 μM, rising to 182 μM when ketosis was induced with a biguanide (300 mg/kg/day metformin), but falling to 155 μM when pioglitazone (1 mg/kg/day) was co-administered with the metformin. Preferred ketosis:

Dwg.0/0

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on STN

2000194197 EMBASE **Insulin sensitizers and polycystic ovary syndrome: Can a diabetes medication treat infertility?**.

Kim L.H.; Taylor A.E.; Barbieri R.L.. Dr. L.H. Kim, Department of Obstetrics/Gynecology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, United States. Fertility and Sterility 73/6 (1097-1098) 2000.

Refs: 4.

ISSN: 0015-0282. CODEN: FESTAS.

Publisher Ident.: S 0015-0282(00)00540-9. Pub. Country: United States.

Language: English.

L66 ANSWER 29 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2000282595 EMBASE New approaches in the **treatment** of type 2 diabetes. Zhang B.B.; Moller D.E.. B.B. Zhang, Dept. of Molecular Endocrinology, Merck Research Laboratories, 126 East Lincoln Avenue, Rahway, NJ 07065, United States. Current Opinion in Chemical Biology 4/4 (461-467) 2000.

Refs: 50.

ISSN: 1367-5931. CODEN: COCBF4. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Type 2 diabetes is a chronic metabolic derangement that results from defects in both insulin action and secretion. New **thiazolidinedione insulin sensitizers** have been recently launched. New approaches with mechanisms different from

current therapies are being explored, including novel ligands of peroxisome proliferator-activated receptor, glucagon receptor antagonists, dipeptidyl peptidase IV inhibitors, and insulin receptor activators.

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on STN

2000164613 EMBASE Insulin sensitizers and antiandrogens
in the treatment of polycystic ovary syndrome.

Diamanti-Kandarakis E.; Zapanti E.. E. Diamanti-Kandarakis, Zefyrou 1a,
14578 Ekali, Greece. Annals of the New York Academy of Sciences 900/-
(203-212) 2000.

Refs: 64.

ISSN: 0077-8923. CODEN: ANYAA. Pub. Country: United States. Language:
English. Summary Language: English.

AB The heterogeneous origin of polycystic ovary syndrome (PCOS) has been demonstrated by several studies. Abnormalities in steroidogenesis and metabolism are present, but the exact link between these two pathologic features remains to be clarified. In clinical practice, more than one therapeutic approach for the treatment of this syndrome has been proposed over the last few decades. Because hyperandrogenism and hyperinsulinemia contribute to a different degree to the phenotype of PCOS, therapeutic efforts have focused on agents that could treat or modify the clinical manifestations of these disorders. Antiandrogens as a sole treatment or combined with oral contraceptives are considered the treatment of choice for the manifestations of hyperandrogenemia, but there is no agreement about their efficacy on the metabolic sequelae of PCOS (insulin resistance, hyperinsulinemia, dislipidemia). Furthermore, the improvement of insulin sensitivity by insulin sensitizers may be of therapeutic value directly and/or indirectly in the management of clinical manifestations of hyperinsulinemia and hyperandrogenemia.

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on STN

1999182630 EMBASE Switching insulin-sensitizing agents in patients with type 2 diabetes who require insulin [9]. Blonde L.; Sandberg M.I.; Guthrie R.D. Jr.. Dr. L. Blonde, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, LA 70121, United States. lblonde@ochsner.org. Diabetes Care 22/6 (1004-1006) 1999.

Refs: 11.

ISSN: 0149-5992. CODEN: DICAD2. Pub. Country: United States. Language:
English.

L66 ANSWER 32 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

1999110506 EMBASE Insulin resistance: Site of the primary defect or how the current and the emerging therapies work. Kolaczynski J.W.; Caro J.F.. J.W. Kolaczynski, Thomas Jefferson University, Philadelphia, PA 19107, United States. Journal of Basic and Clinical Physiology and Pharmacology 9/2-4 (281-294) 1998.

Refs: 63.

ISSN: 0334-1534. CODEN: JBPPES. Pub. Country: Israel. Language: English.
Summary Language: English.

AB Insulin resistance is one of the cardinal pathophysiological components of the metabolic syndrome, type 2 diabetes, and frequently co-exists with essential hypertension. Although insulin resistance is defined as inadequate target organ (muscle, liver and fat) responsiveness and/or sensitivity to insulin, the primary defect may be located in the target organs themselves or at their remote controller - the central nervous system. One of the ways of resolving this dilemma is studying the mechanisms of action of drugs that have insulin-sensitizing properties. In this brief review we discuss how the

known and potential **insulin sensitizers**:
metformin, appetite suppressants, **thiazolidinediones**,
and the new class of centrally acting antihypertensive drugs, **Il-receptor
agonists**, may work.

- L66 ANSWER 33 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
1995:292031 Document No. 122:71151 Re-evaluation of a biguanide,
metformin: Mechanism of action and tolerability. Sirtori, Cesare
R.; Pasik, Christophe (Institute Pharmacological Sciences, University
Milano, Fr.). Pharmacological Research, 30(3), 187-228 (English) 1994.
CODEN: PHMREP. ISSN: 1043-6618.
- AB A review, with 139 refs. **Metformin** is a biguanide antidiabetic
medication, that has been in use for over 30 yr. Its mechanism of action,
unknown until a few years ago, is now linked to an improved peripheral
sensitivity to insulin, through a stimulated tissue glucose uptake by a
transporter-linked system. Interest in **metformin** has been
revived by the recent observation of a specific activity of this agent on
some of the major traits of the so called "polymetabolic syndrome" (or
"syndrome X"), characterized by: insulin resistance, hypertriglyceridemia,
hypertension and reduced fibrinolytic activity. **Metformin**, in
studies examining one or more of these, has been shown, possibly through its
peripheral **insulin sensitizing** mechanism, to correct
most of the major symptoms characterizing this insulin resistance
syndrome. **Metformin**, similarly to the other biguanide
phenformin, has been rated as potentially dangerous, because of the
possible induction of lactic acidosis, in some cases with a
fatal outcome. **Metformin** is, however, associated with a very low
incidence of lactic acidosis because, differently from
phenformin, it does not undergo liver metabolism and, as a consequence, there
are no high-risk groups, displaying an impaired metabolic handling. In
this review, in addition to an overall evaluation of the more recent data on
the mechanism of action and clin. use of **metformin**, a detailed
clin. anal. of all published cases of lactic acidosis is
provided. These data indicate that the risk in **metformin** use is
negligible, provided that care is taken when prescribing the drug to
patients with suspected clin. risks of lactic acidosis.

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